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Abstract
While vaccination is an effective measure in reducing the risk of bovine respiratory disease complex (BRDC) in cattle, BRDC losses remain significant. Increasing the efficacy of vaccination depends on elucidating the protective immune response to different antigens included in vaccines, determining the best timing for vaccination and understanding the impact of the age of calf on vaccination. This study measured the serum antibodies present in calves following vaccination against four viruses commonly associated with BRDC: bovine viral diarrhea virus 1 and 2 (BVDV1 and BVDV2), bovine respiratory syncytial virus (BRSV), and bovine herpesvirus (BHV1). Serum antibody titers were measured in more than 1600 calves at 3- week intervals starting at time of first vaccination. This first vaccination occurred at weaning for approximately half of the individuals, and three weeks before weaning for the other half. Dam age (years), time of weaning (initial vaccination or booster vaccination), and age of calf within year-season (days within Year-Season) classification all were found to have a significant effect on measured traits such as initial titer and overall response. Increased initial titer was negatively correlated with each response trait (initial, booster, and overall response). Calves that were weaned at initial vaccination had greater overall antibody response to BVDV1 and BVDV2 compared to calves weaned 3 weeks before initial vaccination. In contrast, calves given their initial vaccination 3 weeks before weaning had greater overall antibody response to BRSV and BHV1 compared to calves that were vaccinated at weaning. Furthermore, the circulating antibody titer at which each virus needed to be below for an individual calf to positively respond to vaccination was determined (log base-2 titer of 0.38 for BVDV1, 1.5 for BVDV2, 3.88 for BRSV, 1.5 for BHV1). This information can be used to improve vaccination protocols to allow for a greater response rate of individuals to vaccination and hopefully improved protection.

Keywords
beef cattle, bovine respiratory disease complex, immune response, vaccination, weaning

Disciplines
Agriculture | Animal Sciences | Veterinary Preventive Medicine, Epidemiology, and Public Health

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Evaluation of responses to vaccination of Angus cattle for four viruses that contribute to bovine respiratory disease complex[1,2]

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ABSTRACT

While vaccination is an effective measure in reducing the risk of bovine respiratory disease complex (BRDC) in cattle, BRDC losses remain significant. Increasing the efficacy of vaccination depends on elucidating the protective immune response to different antigens included in vaccines, determining the best timing for vaccination and understanding the impact of the age of calf on vaccination. This study measured the serum antibodies present in calves following vaccination against four viruses commonly associated with BRDC: bovine viral diarrhea virus 1 and 2 (BVDV1 and BVDV2), bovine respiratory syncytial virus (BRSV), and bovine herpesvirus (BHV1). Serum antibody titers were measured in more than 1600 calves at 3-week intervals starting at time of first vaccination. This first vaccination occurred at weaning for approximately half of the individuals, and three weeks before weaning for the other half. Dam age (years), time of weaning (initial vaccination or booster vaccination), and age of calf within year-season (days within Year-Season) classification all were found to have a significant effect on measured traits such as initial titer and overall response. Increased initial titer was negatively correlated with each response trait (initial, booster, and overall response). Calves that were weaned at initial vaccination had greater overall antibody response to BVDV1 and BVDV2 compared to calves weaned 3 weeks before initial vaccination. In contrast, calves given their initial vaccination 3 weeks before weaning had greater overall antibody response to BRSV and BHV1 compared to calves that were vaccinated at weaning. Furthermore, the circulating antibody titer at which each virus needed to be below for an individual calf to positively respond to vaccination was determined (log base-2 titer of 0.38 for BVDV1, 1.5 for BVDV2, 3.88 for

BRSV, 1.5 for BHV1). This information can be used to improve vaccination protocols to allow for a greater response rate of individuals to vaccination and hopefully improved protection.

Key words: beef cattle; bovine respiratory disease complex; immune response; vaccination; weaning

INTRODUCTION

As one of the most costly diseases in the beef cattle industry, Bovine Respiratory Disease Complex (**BRDC**), results in an estimated loss of more than $750 million a year due to morbidity, mortality, reduced growth performance, and reduced carcass quality (Snowder et al., 2007; Irsik, 2010; Van Eenennaam, 2012). Vaccines vary in efficacy (Theurer et al., 2015), resulting in reduced overall herd immunity when calves are grouped in feedlots. Maternally-derived antibodies passively obtained via colostrum are vital for early calf health (Roth, 2008) and assist protection, but present barriers to vaccination. Calves may not mount a vaccination antibody response if maternal antibody levels are too high (Niewiesk, 2014), and if too low, calves may be at risk before vaccination induces protective immunity. As such, vaccination should occur at a time that calves can positively respond, but still remain protected by maternal antibodies.

Environmental stressors are often associated with an altered immune state (Salak-Johnson and McGlone, 2007; Wein et al., 2016). Weaning has been shown to lower the immune response in calves, and therefore may reduce the effectiveness of vaccination depending on its timing (Hulbert and Moisa, 2016).

This study built upon previous work (Downey et al., 2013) with vaccination against Bovine Viral Diarrhea Virus type 2. By examining response to vaccination traits to four viruses associated with BRDC (Bovine Viral Diarrhea Virus type 1 [**BVDV1**], Bovine Viral Diarrhea Virus type 2 [**BVDV2**], Bovine Respiratory Syncytial Virus [**BRSV**], Bovine Herpesvirus [**BHV1**]), it was possible to identify environmental commonalities associated with immune response to vaccination. The objectives were to identify management and environmental factors that 1) that impact the level of BVDV1, BVDV2, BRSV, and BHV1 circulating maternal antibodies at initial vaccination, 2) influence the rate of BVDV1 and BVDV2 maternal antibody decay prior to initial vaccination, and 3) influence response to vaccination against BVDV1, BVDV2, BRSV, and BHV1 to improve vaccination practices.

MATERIALS AND METHODS

Animals

Purebred American Angus calves (n = 2,834) from the Iowa State University herd were utilized for this study. Not all individuals had recorded response to vaccination phenotype records for each of the 4 viral antigens due to samples being analyzed in batches according to contemporary group and differences in time between samples being analyzed for each antigen. Due to these time differences, only a subset of the total herd humber could be used when examining response to vaccination for a given virus. Phenotypic data (body weights, ages, infectious bovine keratoconjunctivitus classification score(Lepper et al., 1992), and weaning status) were collected on each animal when serum samples were taken. Calves were born in either of 2 seasons (spring or fall) across multiple years (2006 to 2012, 2014). The number of calves with recorded measurments was on average about 350 per year, with more individuals in the spring season compared to the fall season. The only exceptions to this were years 2012 and

2014, in which only spring born calves had measurements and the average number of calves was 226 per year.

Vaccination

Calves were vaccinated with a modified live vaccine (Bovi-Shield Gold 5, Zoetis). This vaccine contained antigens of 4 viruses that are associated with bovine respiratory disease: BVDV1, BVDV2, BRSV, and BHV1. Bovine parainfluenza 3 virus was also part of the modified live vaccine but was not included in this study. The vaccine was administered per manufacturers recommendation to the calves at 2 separate time points, designated initial vaccination (week 0) and booster vaccination (week 3). Calves were given the initial vaccine either at the time of weaning or 3 weeks prior, which resulted in weaning at booster vaccination. This was done to evaluate the effect of weaning as a stressor on response to vaccination. (Figure 1).

Dams of the calves studied received standard herd vaccinations during the course of this study. They received vaccinations approximately 40 days prior to breeding, and again at pregnancy check in the fall. These timings would have had negligible effects on circulating maternal antibodies for the calves studied.

Serum sample collection

Serum samples were collected at 3 time points. The first sample was collected at initial vaccination (week 0), the second sample was collected at booster vaccination (week 3), and the third sample was collected 6 weeks after initial vaccination. Additionally, a subset of the total population used for this study had serum samples collected 3 weeks prior (week -3) to the initial vaccination (subset n = 622 for BVDV1, n = 1,137 for BVDV2). Blood was collected from the

jugular and allowed to coagulate overnight at 4 C. Tubes were centrifuged, after which serum was collected and separated into multiple 1.5 ml tubes and frozen at -20 C.

Viral neutralization

Viral neutralization (VN) assays were performed to quantify the level of neutralizing antibodies present in serum against 4 viruses: BVDV1, BVDV2, BRSV, BHV1. Viral neutralization assays used the following virus strains, cytopathic BVDV1 strain Singer, cytopathic BVDV2 strain A125-C (both obtained from the National Animal Disease Center, USDA-ARS, Ames, IA) BRSV strain ATCC VR-794 and BHV1 strain Cooper (both obtained from National Veterinary Services Laboratory, Ames IA)(Fulton et al., 2000). Viral neutralization assays were performed as previously described (Downey et al., 2013)(Bolin and Ridpath, 1990) with a few modifications between viruses. For BVDV1, 5 replicates were tested for each serum sample. For BVDV2, 5 replicates were tested for each serum sample for animals born before 2014, and 3 replicates were tested for individuals born in 2014. All serum samples were diluted 1:4 to 1:2048. For the BRSV and BHV1 assays 2 replicates were tested for each serum sample and serum samples were diluted between 1:8 and 1:2048. Two-fold dilutions of serum were done using phosphate-buffered saline. The titer was recorded for each calf as the log base 2 reciprocal of the greatest dilution at which neutralizing antibodies were detected. A cell control and viral control were run alongside BVDV1 and BVDV2. A cell control, positive serum control, and negative serum control were run for BRSV and BHV1. Antibody titer score was recorded as the average log base 2 reciprocal of the greatest dilution that neutralized virus across 5 replicates. A modified calculation was done for samples with 3 replicates. An average log base 2 reciprocal was taken across the 2 replicates for BHV1 and BRSV. If all wells within the first dilution showed a cytopathic effect, a titer score of 0 was given for the calf. Not all samples were

available for analysis for antibodies to each of the 4 viruses, which resulted in different subsets of individuals being tested for each virus.

Response traits

Seven antibody titer traits were analyzed. Maternal Antibody Titer Level at week -3 and Maternal Decay (MD; rate of change between week -3 and week 0) were only analyzed for BVDV1 (622 head) and BVDV2 (1137 head). Maternal antibody decay (MD) was defined as the difference between week -3 and week 0 divided by the difference in calf age between the 2 serum collection dates (average calf age difference: 22 days for both BVDV1 and BVDV2). This was not exactly 21 days for each calf as all individuals in a single location had samples taken at the same time to minimize number of times interacting with the herd.

Initial Antibody Titer Level was defined as the log base 2 antibody titer score observed at week zero. Initial Vaccination Response (**IVR**) was defined as the difference between antibody titer level observed at week 3 (booster vaccination time point) vs. week 0 (initial vaccination time point). Booster Vaccination Response (**BVR**) was defined as the difference in antibody titer level observed between week 6 (booster response time point) and week 3 (booster vaccination time point). Overall Vaccination Response (**OVR**) was defined as the difference in antibody titer level observed between week 6 (booster response time point) and week 0 (Initial vaccination time point). Final Antibody Titer Level was defined as the log base 2 antibody titer score observed at week 6 (Tait et al., 2013) (Fig. 1).

Statistical analysis

Environmental and systemic factors were evaluated to determine their potential effect on response to vaccination traits. Year-season classification were considered a single variable for

the purpose of this study, as previously described (Downey et al., 2013). Age within year-season was fit as a covariate. Additional contemporary group categories (date of serum batch analyzed, lab technician analyzing data, farm) were fit as covariates, but showed no statistical significance.

Pre and initial antibody titer levels were analyzed using the following statistical model:

$$y_{ijklm} = \mu + YS_i + DA_J + Sex_k + ID_l + BW_m + A_m(YS_i) + e_{ijklm}$$

$$Model\ 1$$

Where y_{ijklm} was the pre or initial antibody titer for calf m. μ = overall mean, YS_i = year-season classification [i = 2006 S, 2006 F, 2007 S, 2007 F, 2008 S, 2008 F, 2009 S, 2009 F, 2010 S included for BVDV1, BRSV and BHV1. 2010 F included for BVDV1. 2011 S, 2011 F, 2012 S, 2014 S but not 2006 S and 2006 F included for BVDV2], DA_J = dam age [j = 2 to 11 years of age. Ages 12 to 14 included for BVDV2], and Sex_k = calf sex (k = bull, steer, or heifer) were fit as fixed effects in the model. ID_l = Dam ID for calf m, which was fit as a random effect to account for multiple progeny. BW_m = Birth weight for calf m and $A_m(YS_i)$ = calf age at pre or initial vaccination time point within year-season classification were fit as covariate effects. e_{ijklm} = error term which was assumed to be normally distributed (mean = 0, variance = $\sigma^2 e$). Variables were removed from the model systematically until only variables with $P < 0.05$ remained in the models. This resulted in a model with only significant factors and ID_l.

Maternal antibody decay rate was analyzed using the following statistical model:

$$y_{ijklm} = \mu + YS_i + DA_J + Sex_k + ID_l + A_m(YS_i) + T_m + e_{ijklm}$$

$Model\ 2$

Where y_{ijklm} was the maternal antibody decay rate in titer level per day for calf m. μ =overall mean, YS_i = year-season classification [i = 2006 S, 2006 F, 2007 S, 2007 F, 2008 S, 2008 F, 2009 S, 2009 F, 2010 S included for BVDV1, BRSV and BHV1. 2010 F included for BVDV1. 2011 S, 2011 F, 2012 S, 2014 S but not 2006 S and 2006 F included for BVDV2], DA_J = dam age [j = 2 to 11 years of age. Ages 12 to 14 included for BVDV2], and Sex_k = calf sex (k = bull, steer, or heifer) were fit as fixed effects in the model. ID_l = Dam ID for calf m, which was fit as a random effect to account for multiple progeny. $A_m(YS_i)$ = calf age at pre-vaccination within year-season classification and T_m = pre-vaccination antibody titer level for calf m were fit as covariate effects. e_{ijklm} = error term, which was assumed to be normally distributed (mean = 0, variance = $\sigma^2 e$). Variables were removed from the model systematically until only variables with $P < 0.05$ remained in the model. This resulted in a model with only significant factors and ID_l.

Response to vaccination traits (IVR, BVR, OVR, Final antibody titer) were analyzed using the following statistical model:

$$y_{ijklmno} = \mu + YS_i + Sex_J + W_k + PE_l + DA_m + ID_n + T_o + (T_o x T_o) + A_o(YS_i) + ADG_o + e_{ijklmno}$$

$Model\ 3$

Where $y_{ijklmno}$ = IVR/BVR/OVR or final antibody level measured on calf o. YS_i = year-season classification [i = 2006 S, 2006 F, 2007 S, 2007 F, 2008 S, 2008 F, 2009 S, 2009 F, 2010 S included for BVDV1, BRSV and BHV1. 2010 F included for BVDV1. 2011 S, 2011 F, 2012

S, 2014 S but not 2006 S and 2006 F included for BVDV2], Sex_J = calf sex (k = bull, steer, or heifer), W_k = weaning time (k = weaned at initial or booster vaccination), PE_l = pinkeye classification at weaning (l = 0 for unaffected, 1 for affected), and DA_m = dam age [j = 2 to 11 years of age. Ages 12 to 14 included for BVDV2] were fit as fixed effects in the model. ID_l = Dam ID for calf m, which was fit as a random effect to account for multiple progeny. T_o = initial antibody level for calf o for IVR/OVR/final antibody level and booster antibody level for BVR, $(T_o x T_o)$ = quadratic effect for IVR/OVR/final antibody level and booster antibody level for BVR, $A_o(YS_i)$ = calf age at vaccination (o = calf age at week 6 for final antibody level, age at initial vaccination for IVR and OVR, and age at week 3 for BVR) within year-season classification, and ADG_o = average daily gain for each of the 3 response variables (not fit for final antibody level) were fit as covariate effects. $e_{ijklmno}$ = error term which was assumed to be normally distributed (mean = 0, variance = $\sigma^2 e$). Variables were removed from the model systematically until only variables with $P < 0.05$ remained in the models. This resulted in a model with only significant factors and ID_l.

Clustering

Clustering of animals within a given virus category was done with SSClust3.0 (Ma et al., 2006). The program was run with a chain number of 5, threshold of 0.1, and a cluster number of 2+ for each population of individuals for each of the 4 viruses. Visual outputs from clustering analysis allowed for identification of subgroups of calve that responded differently to vaccination across the course of the study.

RESULTS

The average age at initial vaccination was 138 days for BVDV1, 127 days for BVDV2, and 136 days for BHV1 and BRSV (SD = 31.3, 35.2, 29.6 in days). Average weight of calves at initial vaccination was 145.45 kg for BVDV1, 139.48 kg for BVDV2, and 150.51 kg for BRSV and BHV1 (SD = 5.1, 5.6, 5.1, respectively). Average age and weight of calves varied among the different antigens due to differences in the number of individuals with recorded serum titers for each antigen, which resulted in different total numbers of calves for each antigen group. The proportion of male calves to female calves was relatively equal, with males being slightly more common (males = 864 for BVDV1, 1191 for BVDV2, and 849 for BRSV and BHV1; females = 791 for BVDV1, 1041 for BVDV2, and 783 for BRSV and BHV1). Table 1 shows the number of animals tested for antibodies against each virus per time point, as well as the mean, standard deviations and range for antibody titer, body weight, and age at each time point.

Pre-vaccination and initial vaccination antibody titers were affected by Year-season, Dam age, Birth weight, and Age within year-season (Table 2). Dam age was positively correlated with increased initial titer levels for all viruses with the exception of BHV1 (Fig. 2). For BVDV1, maternal antibody titer increased as dam age increased up to 8 years of age. The spike in maternal antibody titer was likely due to the large standard error that resulted from low numbers of representative dams at this age. BVDV2, BRSV and BHV1 titer levels increased as dam age increase up to 7 years of age. Initial antibody titers decreased ($P < 0.05$) as calf age increased although at varying rates between the 4 viruses (Fig. 3).

Maternal decay

Maternal antibody decay rate was evaluated for BVDV1 and BVDV2. No pre-vaccination data was collected for BRSV or BHV1, so the rate of decay of serum antibody before the first vaccination could not be determined. Year-season classification, Dam age, Sex, Age within year-season classification, and Pre-vaccination levels significantly affected the decay rate of BVDV2 maternal antibody level. For BVDV1 only Dam age, Age within year-season, and Pre-vaccination levels were significant (Table 2). The rate of decay of BVDV1 maternal antibody level generally decreased as dam age increased. In contrast, the rate of decay of BVDV2 maternal antibody level remained relatively constant across dam age (Table 3). Calf age was inversely correlated with rate of decay for both BVDV1 and BVDV2, with older calves having a greater rate of decay than younger calves (Fig. 4). For BVDV1 and BVDV2, pre-vaccination maternal antibody titers were inversely correlated with rate of decay. A 1 unit increase in prevaccination maternal antibody titer corresponded to a 0.01698 titer units/day decrease in maternal antibody decay rate for BVDV1 and 0.01139 titer units/day for BVDV2 ($P < 0.0001$).

Response to vaccination

Response to vaccination may be influenced by factors other than circulating maternal antibodies. Thus, other environmental factors were evaluated for their effect on initial response to vaccination, booster response to vaccination, overall response to vaccination, and final antibody titer. All factors in Model 3 were tested, and results can be found in Table 4. Sex was only significant for initial vaccination titer for BRSV. Average daily gain of the calf was only significantly associated with the initial response of BVDV1 vaccination. The observed baseline titer, i.e. the antibody titer at the first time point used to calculate a vaccination trait (e.g. the titer

at week 0 for IVR, OVR, and Final Antibody titer, or the week 3 antibody titer for BVR) was significant for every trait with the exception of the final antibody titer for BRSV and the IVR for BVDV1. Age within year-season classification was significant for all traits. Weaning date was significant for many traits, and individuals were classified as either weaned at week 0 or week 3. Weaning classification was associated with increased overall antibody response to BVDV1 and BVDV2 when calves were weaned at initial vaccination. Weaning classification was also associated with increased OVR in BRSV and BHV1 when calves were weaned at booster vaccination (see for example results for calves receiving initial vaccination at weaning and having a dam aged 5 years old, in Fig. 5). Pink eye occurrence was statistically significant for only a few time points across all 4 viruses (BVDV1 Final titer level; BVDV2 IVR, OVR, Final titer level; BHV1 IVR).

The effect of calf age at first vaccination within year-season classification was averaged across all year-seasons for a given virus and time point, and compared between the 4 viruses. This was done to help account for birthing conditions that can vary considerably between spring and late summer/early fall in the Midwest United States. For initial vaccination response, an increase in calf age resulted in a lower IVR for all viruses with the exception of BVDV1, which increased slightly as calf age increased (Fig. 6a). Booster vaccination response increased with calf age for all 4 viruses (Fig. 6b). Overall vaccination response increased with calf age for all viruses, with the exception of BRSV, which resulted in a slight decrease in OVR with increased age (Fig. 6c). Final titer increased with calf age for BVDV1 and BVDV2, yet decreased with age in BRSV and BHV1 (Fig. 6d). Supplemental Figures 1 to 4 show the aforementioned trends when not averaged across year-seasons.

The observed baseline titer, i.e. the antibody titer at the start of a response to vaccination trait (e.g. titer score at week 0 for IVR, OVR, and final antibody titer, or week 3 antibody titer for BVR) was also averaged across all year-season classifications and compared between the 4 viruses (Fig. 7). Supplemental Figures 5 to 8 show the same trends but not averaged across year-season. For all 4 response to vaccination traits (IVR, BVR, OVR and final antibody titer level) antibody titer decreased as their respective baseline titer increased. To have a positive initial vaccination response, initial antibody level (week 0) needed to be below 1.5 for BVDV2 and BHV1, but below 0.38 for BVDV1 and 3.88 for BRSV (Fig. 7a). To have a positive booster vaccination response, the week 3 antibody level needed to be below 1.73 for BVDV1, 3.32 for BVDV2, 4.50 for BRSV and 2.38 for BHV1 (Fig. 7b). To have a positive overall vaccination response, week 0 antibody level needed to be below 1.55 for BVDV1, 2.71 for BVDV2, 4.12 for BRSV and 1.29 for BHV1 (Fig. 7c). Final antibody titer decreased for all viruses as week 0 antibody concentration increased. BRSV also saw a decrease in final antibody titer as week 0 antibody concentration increased, but at a slow decline compared to the other 3 viruses, with a theoretical final antibody titer score of zero only when initial antibody levels are at 184.92 titer units (Fig. 7d). Figures 6 and 7 show trends for calves aged 55 to 200 days of age, although the true age range for each virus at each time point can be seen in Table 1.

The overall antibody titer level trend was plotted for each virus across the 3 (or 4) serum collection time points (Fig. 8). The overall trend was fit utilizing model 1, and all non-significant factors were removed before being fit. Each time point had age within year-season classification fit as the average age of calves with records. For BVDV1 and BVDV2, sex and birth-weight were included in the final model, while for BRSV and BHV1 they were not significant. Titers to

BVDV1 and BVDV2 were observed to decrease from week -3 to week 3, and then increase from week 3 to week 6. Titers to BRSV and BHV1 increased from week 0 to week 6.

Titer curves for each virus across all individuals are shown in Fig. 9. Average titer across time is plotted as green lines, while individuals were plotted as grey lines. Fig. 10 shows the titer curves for individual animals that had a titer of 0 for BVDV1, BVDV2, and BHV1 at week 6. BRSV was included for the sake of comparison by plotting only individuals with a final titer level of 3, as no individual failed to seroconvert for BRSV at week 6. There were 367, 100 and 468 calves that had a titer of 0 at week 6 against BVDV1, BVDV2 and BHV1, respectively.

Of the 367 individuals that had a final titer of 0 for BVDV1, 107 of these calves had a titer of 0 at all time points, 119 calves did not obtain a titer of 0 until week 6, 96 calves had a titer of 0 by week 3, 19 calves obtained and maintained a titer of 0 by week 0 (required pre-vaccination data), while 26 calves exhibited titers that oscillated or had missing data at weeks 0 or 3. Of the 100 individuals that had a final titer of 0 for BVDV2, 9 of these calves had a titer of 0 at all time points, 57 calves did not obtain a titer of 0 until week 6, 27 calves had a titer of 0 by week 3, 3 calves obtained and maintained a titer of 0 by week 0 (required pre-vaccination data), while 4 calves exhibited titers that oscillated or had missing data at weeks 0 or 3. Of the 468 individuals that had a final titer of 0 for BHV1, 227 of these calves had a titer of 0 at all time points, 62 caves did not obtain a titer of 0 until week 6, 70 calves had a titer of 0 by week 3, 109 calves obtained and maintained a titer of 0 by week 0 (required pre-vaccination data), while 109 exhibited titers that oscillated or had missing data at weeks 0 or 3. Oscillating titers for these plots was defined as a titer change from positive/0/positive, or from 0/positive/0 at some point across all measurement time points. 132 individuals for BRSV were shown who had a final titer of 3 (the lowest recorded titer score at week 6).

Titer trends for each virus were plotted across time with SSClust3.0 (Ma et al., 2006). The mean curve for each cluster was obtained and plotted as a black line, alongside a 95% confidence interval in red. Curves for the four clusters within BVDV1 can be seen in Fig. 11. Interpolation between time points can be seen between each of the 4 time points (pre-vaccination [-3], initial vaccination [0], booster vaccination [3], and booster response [6]). The y-axis represents proportional titer level compared to a base level of 1 determined by SSClust3.0 for each cluster. Additional trends for the other 3 viruses can be found in supplemental Figures 9 to 11.

DISCUSSION

An individual's titer can be indicative of immunological health, and therefore may be useful for determining which individuals are more responsive to vaccination protocols and thus better contributors to herd immunity in livestock (Sharma et al., 2016). By utilizing 4 viruses commonly associated with BRDC, we showed that there are various factors that impact response to vaccination in pre-feedlot calves, and that these factors may not be the same for all viruses. While we only measured responses to all 4 viruses from 1,273 calves, for some viruses we report results for more calves when they were available. The inclusion of additional data from more calves did not significantly alter observed results.

Maternally-derived antibodies serve an important purpose in protection for calves during their early developmental lifetime, but the suppressive effects of maternal antibodies on vaccination may hamper the ability to determine the calf's own immunological response for an individual as measured by seroconversion (Fulton et al., 2004; Guzman and Taylor, 2015). Maternal antibody decay was examined for both BVDV1 and BVDV2 by determining the rate of decay in antibody titer from 3 weeks before initial vaccination to the initial vaccination at week

0. The rate of decay for BVDV2 titers were always greater than for BVDV1 titers at a given calf age, although the change in rate of decay as calves aged was greater for BVDV1 than for BVDV2. The greater rate of decay of BVDV2 was likely due to greater average maternal antibody titer levels compared to BVDV1 (O'Neill et al., 2006). It may also be due in part to fewer calves (622) with pre-vaccination data for BVDV1 than the number with prevaccination data for BVDV2 (1137), however this is purely speculative in nature. The rate of maternal antibody decay increased with calf age, which was consistent with other studies on maternal circulating antibodies (Kirkpatrick et al., 2008), and followed closely with a previous work examining maternal decay and BVDV2 titers (Downey et al., 2013). Rates of decay for both BVDV1 and BVDV2 indicated that by initial vaccination at week 0, many individuals had low enough circulating maternally-derived antibodies to mount a resonse to vaccination. The level of circulating maternally-derived antibody was directly related to calf and dam age. Higher birthweights were found to be significantly associated with higher maternally-derived antibody levels at initial vaccination, although their actual effect was minor compared to other factors. All discussion on observed response to vaccination must be tempered with the knowledge that circulating maternally-derived antibodies may still have been binding to antigens. Therefore, the observed responses may have been different if calves had no maternal antibodies at the time of vaccination.

Weaning has been associated with increased stress in calves, and stress has been implicated in negatively affecting the immune response of individuals (Hulbert and Moisa, 2016). To determine the effect of weaning stress, approximately half of the calves used for this study were weaned at initial vaccination (week 0) with the other half weaned at booster vaccination (week 3). Results indicate that titers to BVDV1 and BVDV2 increased significantly

more when calves received their initial vaccination at the time of weaning; in contrast, titers to BHV1 and BRSV increased significantly more when calves received their initial vaccination 3 weeks before weaning. However, it is important to remember that titers for different calves were included in the model describing the responses to BVDV1/BVDV2, and BHV1/BRSV. Thus it may not be valid to make a comparison between the responses to BVDV1/BVDV2 and BRSV/BHV1. The same calves were included in the models describing BRSV and BHV1, so comparison between the responses to those viruses may be more appropriate.

A decrease in initial antibody titer score for BVDV1 and BVDV2 was likely linked to greater baseline titer values, i.e. the antibody titer score at week 0, compared to BRSV and BHV1. Increased calf age was associated with greater overall vaccination response for all viruses with the exception of BRSV (rate of titer score increase as calf age increased was different for BVDV1, BVDV2 and BHV1). This was in agreement with a previous study which focused solely on BVDV2 (Downey et al., 2013). The decrease in initial antibody titer is understandable as the lower maternal antibodies found in older individuals would allow for the immune system to respond with increased antibody production to the presence of viruses (Munoz-Zanzi et al., 2002). For an antibody response to be mounted in the presence of viral antigens, it appears that an individual's circulated antibodies to that antigen must be below a specific threshold. If circulating antibodies are above this threshold, they may bind the viral antigens while reducing stimulation of the individual's immune system, as seen by decreasing titer levels for individuals with high initial vaccination titers. Changes in trends for each response variable as base titer level increased (e.g. titer score at week 0 for IVR, OVR, and Final antibody level or week 3 antibody titer level for BVR) were obtained to assist in identifying antibody response in relation to a respective antibody level at a given time. The intersection of the trend line with x-axis

indicates an observed titer level at which an individual would positively respond to the presence of the virus if circulating antibodies were below the x-value of the intersection, or fail to respond if circulating antibodies were above that value. For BVDV1 and BVDV2, the threshold was 0.38 and 1.5 log-base 2 titer, which explains the initial titer score decrease from week 0 to week 3 observed in BVDV1 and BVDV2.

The BRSV titer values remained relatively constant across calf age for all response variables, indicating that there would be a response at any calf age. While it was not possible to confirm an exact reason for this behavior, it may be due to the ubiquitous nature of BRSV in the environment (Ellis et al., 2005). This would indicate that most calves had already been exposed to BRSV at some point in their early life, and as such already have the ability to generate antibodies in the presence of the BRSV antigen. This indicated that calves, on average, were always able to respond to the presence of BRSV antigens and that vaccination may not be responsible for these observations.

This ubiquitous nature of BRSV may also explain why every calf seroconverted by week 6 for BRSV. The lowest recorded final antibody titer for BRSV was 3 on the log base-2 scale, while BVDV1, BDVD2, and BHV1 all had some proportion of individuals with a final antibody titer of 0. The minimum possible record above 0 does differ between the four viruses, as BRSV and BHV1 had only 2 assay replicates done per viral neutralization dilution compared to the 3 or 5 assay replicates for BVDV1 and BVDV2. This would only allow BRSV and BHV1 to have final titers between 1.7 and 3 at a minimum, however it would not prevent final titers of 0 as seen in BHV1 observations. Again, the likely presence of BRSV throughout the herd is the most probable cause for why some animals did not seroconvert for the other 3 viruses but every individual measured for antibody response to BRSV managed to seroconvert.

A large amount of variation was found to be present in vaccine responses between individuals, leading to the question of if there were clusters of individuals who exhibited similar responses to vaccination. Average titer trends and the 95% confidence interval for each virus was plotted with SSClust3.0, which identified subsets of individuals (clusters) who exhibited similar responses to selection. These clusters may indicate differences of within herd antibody production or immune system strength, as some clusters appeared to respond less robustly than others.

For the proportion of individuals who did not seroconvert by week 6 to BVDV1, BVDV2, and BHV1, there are individuals who never seroconvert at any time point, and those who had recorded antibody titers that dropped to 0 at some time period after the first measurement. The most interesting individuals are those that never seroconvert despite having maternal antibodies and 2 rounds of vaccination. There were 107 individuals who never seroconverted to BVDV1, 9 individuals that never seroconverted to BVDV2, and 227 individuals that never seroconverted to BHV1. This is 6.5%, 0.4%, and 13.9% of the respective set of animals with records for the given virus studied who failed to seroconvert. One calf failed to seroconvert for both BVDV1 and BVDV2, and 12 calves failed to seroconvert for both BVDV1 and BHV1. There were no calves that failed to seroconvert for both BVDV2 and BHV1, and consequently no calves that failed to seroconvert for all 3 viruses. Growth traits did not significantly differ between animals who seroconverted and those who did not, indicating that development of the calves was not hindered by a lack of immune response up to the point at which serum samples were collected. Although individuals who did not seroconvert still grew normally and may be protected in herds due to herd immunity, these would be the most at risk

individuals and therefore likely the ones to be culled so as to potentially reduce morbidity incidence in the herd.

To address methodology, a reduction in assay replicates occurred in later years of BVDV2 (5 to 3 replicates). Additionally, BHV1 along with BRSV were analyzed with only 2 replicates as opposed to 5. While reduction in assay replicates is likely to reduce overall accuracy of recorded measurements, this was done to improve statistical power by increasing the number of individuals with measured serum levels. By improving our power to statistically analyze observed measurements, we are able to better estimate trends in the population. This does lower the ability to analyze individuals on a one-by-one basis, however this is not the goal of this particular study.

In summary, an individual's response to vaccination was influenced by multiple factors, including initial maternally-derived circulating antibodies, time of weaning, and age of the calf. When these factors are considered together, it indicates that calves have on average a more positive response to vaccination when they are older, likely due to a reduced quantity of circulating maternally-derived antibodies. Time of weaning relative to initial vaccination impacted overall response to vaccination for a given virus. Individuals with recorded BVDV1 and BVDV2 titers had more robust overall antibody responses when initially vaccinated at the time of weaning, while individuals with recorded BRSV and BHV1 titers had more robust overall antibody response to vaccination when weaned 3 weeks after that initial vaccination. This difference in robustness of response to vacciantion indicates that the stress associated with weaning impacts response to vaccination differently for different viruses. It is still important to note that not all individuals had titers recorded for all 4 viruses, and therefore direct response comparisons cannot be made for every individual and can only be made based on overall herd

averages. A proportion of the calf population was identified as non-responders or individuals who failed to seroconvert at week 6. No reduced growth or development was associated with that proportion of individuals at the time of serum collection, possibly due to the effect of herd immunity. Genomic analysis of these individuals will be important, however, due to their potentially weaker genetics in respect to antibody production. All of this together helps develop a more beneficial direction under which vaccinations could be administered.

Figure Captions:

Figure 1: Timeline of serum sample collection. Pre-vaccination time point (-3 weeks) samples were only tested for BVDV1 and BVDV2.

Figure 2: Average initial antibody concentration by dam age in years for A) BVDV1, B) BVDV2, C) BRSV and D) BHV1. Pre-vaccination titers by dam age included for BVDV1 and BVDV2. Different letters indicate significantly different dam ages at $P < 0.05$.

Figure 3: Initial antibody titer (week 0) by calf age in days, averaged across year-season classification for BVDV1, BVDV2, BRSV and BHV1 and extrapolated between 50 and 200 days of age.

Figure 4: Weighted Average of Maternal antibody decay rate (titer unit/day) by prevaccination age of calf for BVDV1 and BVDV2 and extrapolated between 50 and 200 days of age.

Figure 5: Change in average overall antibody response by weaning time point for BVDV1, BVDV2, BRSV and BHV1. Significant differences between weaning classification represented with different letters above error bars.

Figure 6: Estimated response traits and final antibody titer by calf age in days for BVDV1 (n =1654), BVDV2 (n = 2231), BRSV (n=1631), BHV1 (n=1631). A) Initial vaccination response, B) Booster vaccination response, C) Overall vaccination Response, D) Final Antibody Titer. Covariates of weaning at initial vaccination, Pink Eye = yes, dam age = 5 years. Slope indicates weighted average effect of age; vertical shift indicates weighted average year-season effect.

Figure 7: Response traits and final antibody titer normalized by starting titer for BVDV1 (n =1654), BVDV2 (n = 2231), BRSV (n=1631), BHV1 (n=1631). A) Initial vaccination response,

B) Booster vaccination response, C) Overall vaccination Response, D) Final Antibody Titer. Covariates of weaning at initial vaccination, Pink Eye = yes, dam age = 5 years. Slope indicates weighted average effect of base titer; vertical shift indicates weighted average year-season effect.

Figure 8: Average titer over time for each of four viruses. Trend fit using model 1 and removing any non-significant factors.

Figure 9: Titers across serum collection time points. A) BVDV1 (n =1654), B) BVDV2 (n = 2231), C) BRSV (n=1631), D) BHV1 (n=1631). Average titer level plotted in green, all individuals plotted in grey.

Figure 10: Individuals with a final titer of zero. A) BVDV1 (n = 367), B) BVDV2 (n = 100), C) BHV1 (n = 468). Average titer level across all individuals measured is plotted in green. D) BRSV (n = 132) shows individuals with the minimum titer calculated at week six (3 on a log base-2 scale). While it is not the same trend as shown in A, B and C, it was included to allow comparison.

Figure 11: Trends within individuals with measured BVDV1 data. Four clusters were generated, with n = 163 calves for cluster 1, n = 524 calves for cluster 2, n = 136 calves for cluster 3, and n = 809 calves for cluster 4. X-axis shows titer measurement time points (pre-vaccination, initial vaccination, booster vaccination, and booster response). Y-axis represents average titer of cluster, calculated proportional to other time points, with a score of 1 being the reference. Black lines represent mean titer trends; red lines represent 95% confidence interval.

Table 1: Means for titer, calf age, and calf weight at four time points for Bovine Viral Diarrhea Virus 1 (BVDV1), Bovine Viral Diarrhea Virus 2 (BVDV2), Bovine Respiratory Syncytial Virus (BRSV), and Bovine Herpesvirus 1 (BHV1)

BVDV1	Calf Number	Titer, log base-2	Range	SD	Age, days	SD	Range	BW, kg	SD
Pre-vaccination[1]	622	2.68	(0-12.3)	2.68	111.8	27.9	(28-169)	133.4	30.6
Initial Vaccination	1,648	2.14	(0-10.5)	2.15	138.0	29.4	(54-205)	149.2	34.5
Booster Vaccination	1,488	1.5	(0-9.3)	1.7	158.6	29.7	(76-229)	173.8	39.7
Final	1,348	2.3	(0-9.3)	1.8	177.9	29.1	(99-250)	190.1	40.0
Decay, titer/day[2]	622	-0.023		0.06					
BVDV2									
Pre-vaccination[1]	1,137	4	(0-10.5)	2.32	109.1	28.7	(28-165)	145.3	34.1
Initial Vaccination	2,177	3.24	(0-11.2)	2.38	127.0	35.0	(30-205)	143.2	37.5
Booster Vaccination	1,927	2.5	(0-11.3)	1.98	152.9	31.4	(57-229)	164.3	39.7
Final	1,917	4.17	(0-9.16)	1.91	174.9	30.9	(78-250)	182.3	42.6
Decay, titer/day[2]	1,137	-0.041		0.045					
BRSV									
Initial Vaccination	1,632	1.08	(0-6)	1.81	136.3	29.6	(53-205)	150.5	36.1
Booster Vaccination	1,310	3.73	(3-6)	0.81	151.1	28.0	(76-229)	170.9	39.1
Final	1,483	5	(3-6.46)	0.89	177.3	35.0	(99-250)	189.5	40.3
BHV1									
Initial Vaccination	1,621	0.87	(0-6)	1.45	136.3	29.6	(53-205)	150.3	36.1
Booster Vaccination	1,351	2.1	(0-6)	1.79	156.8	29.7	(76-229)	170.4	38.9
Final	1,377	2.98	(0-6.58)	2.3	177.5	34.0	(99-250)	189.6	40.2

[1]Viral Neutralization titers to BRSV and BHV1 were not measured in pre-vaccination samples thus results for pre-vaccination and decay are only reported for BVDV1 and BVDV2.

[2]Titer reported as titer/day change for Maternal Decay.

Table 2: Significance for fixed effects relating to initial antibody titer, pre-vaccination antibody titer, and maternal decay for Bovine Viral Diarrhea Virus 1 (BVDV1) and Bovine Viral Diarrhea Virus 2 (BVDV2)[1]

BVDV1	Initial	Pre-vaccination	Decay
Year-Season	<0.0001	0.0012	0.471
Dam Age	<0.0001	<0.0001	0.0012
Sex	0.2431	0.2201	0.9292
Birth Weight	0.0006	0.0012	*****
Age(Year-Season)	<0.0001	<0.0001	0.2002
Pre-vaccination level	*****	*****	<0.0001

BVDV2	Initial	Pre-vaccination	Decay
Year-Season	<0.0001	0.004	<0.0001
Dam Age	<0.0001	<0.0001	0.0012
Sex	0.099	0.3292	0.1383
Birth Weight	<0.0001	0.0136	*****
Age(Year-Season)	<0.0001	<0.0001	<0.0001
Pre-vaccination level	*****	*****	<0.0001

[1]Viral Neutralization titers to BRSV and BHV1 were not measured in pre-vaccination samples, thus results are only reported for BVDV1 and BVDV2.

*****: Variable not tested.

Table 3: Rate of maternal antibody decay by dam age for Bovine Viral Diarrhea Virus 1 (BVDV1) and Bovine Viral Diarrhea Virus 2 (BVDV2)

BVDV1	Dam Age	Rate of Decay	Standard Error
	2[a]	-0.01911	±0.008584
	3[b]	-0.04109	±0.007251
	4[b]	-0.03863	±0.007018
	5[ab]	-0.0339	±0.009137
	6[a]	-0.00956	±0.009723
	7[a]	-0.00958	±0.009905
	8[a]	-0.00292	±0.01236
	9[a]	-0.00307	±0.01422
	10[ac]	0.0232	±0.02755
	11[c]	0.06686	±0.03497

BVDV2	Dam Age	Rate of Decay	Standard Error
	2[a]	-0.06558	±0.004561
	3[b]	-0.05428	±0.003819
	4[b]	-0.04727	±0.003845
	5[b]	-0.05251	±0.004357
	6[bc]	-0.04466	±0.00471
	7[cd]	-0.03717	±0.00474
	8[bde]	-0.0435	±0.005412
	9[ab]	-0.04938	±0.005677
	10[ab]	-0.05465	±0.008574
	11[ce]	-0.02878	±0.00935
	12[abc]	-0.05348	±0.02315
	13[abc]	-0.0683	±0.03974
	14[abc]	-0.0554	±0.03959

[a-e]: Different superscripts indicate significantly different estimates at $P < 0.05$ within a single virus analyzed.

Table 4: Class effects and covariates associated with initial response, booster response, overall response, and final antibody titer for Bovine Viral Diarrhea Virus 1 (BVDV1), Bovine Viral Diarrhea Virus 2 (BVDV2), Bovine Respiratory Syncytial Virus (BRSV), and Bovine Herpesvirus 1 (BHV1)

BVDV1	Initial Response	Booster Response	Overall Response	Final Antibody Level
Year-season	0.05	0.0823	0.0047	<0.0001
Sex	0.3856	0.904	0.984	0.9507
Pink Eye	0.6824	0.2001	0.116	0.013
Dam Age	0.0034	0.0256	0.0024	0.029
Wean	0.2726	0.0526	0.0004	0.0022
Titer	0.2605	<0.0001	<0.0001	<0.0001
Titer*Titer	<0.0001	<0.0001	<0.0001	<0.0001
Age(Year-season)	<0.0001	<0.0001	0.0003	<0.0001
ADG	0.0015	0.7861	0.7427	*****

BVDV2	Initial Response	Booster Response	Overall Response	Final Antibody Level
Year-season	0.0007	<0.0001	<0.0001	<0.0001
Sex	0.8879	0.0573	0.2283	0.2379
Pink Eye	0.0055	0.2236	0.0195	0.0181
Dam Age	0.0518	<0.0001	<0.0001	<0.0001
Wean	<0.0001	0.0746	0.0012	0.0005
Titer	<0.0001	<0.0001	<0.0001	<0.0001
Titer*Titer	<0.0001	<0.0001	<0.0001	<0.0001
Age(Year-season)	<0.0001	<0.0001	<0.0001	<0.0001
ADG	0.3792	0.3478	0.1834	*****

BRSV	Initial Response	Booster Response	Overall Response	Final Antibody Level
Year-season	<0.0001	<0.0001	<0.0001	<0.0001
Sex	0.0311	0.1712	0.2633	0.2362
Pink Eye	0.1375	0.5948	0.766	0.9354
Dam Age	0.6456	0.04	0.0002	<0.0001

Wean	0.5632	<0.0001	<0.0001	<0.0001
Titer	<0.0001	<0.0001	<0.0001	0.4414
Titer*Titer	0.931	0.585	0.1151	0.124
Age(Year-season)	<0.0001	<0.0001	<0.0001	<0.0001
ADG	0.9364	0.1578	0.958	*****

BHV1	Initial Response	Booster Response	Overall Response	Final Antibody Level
Year-season	<0.0001	<0.0001	<0.0001	<0.0001
Sex	0.0751	0.7596	0.4038	0.4557
Pink Eye	0.0128	0.6701	0.6821	0.7563
Dam Age	<0.0001	0.0352	0.0021	0.0002
Wean	0.0004	<0.0001	<0.0001	<0.0001
Titer	<0.0001	<0.0001	<0.0001	<0.0001
Titer*Titer	0.7269	0.8379	<0.0001	<0.0001
Age(Year-season)	<0.0001	<0.0001	<0.0001	<0.0001
ADG	0.3721	0.387	0.2336	*****

*****: Not tested for column trait.

Figure 1:

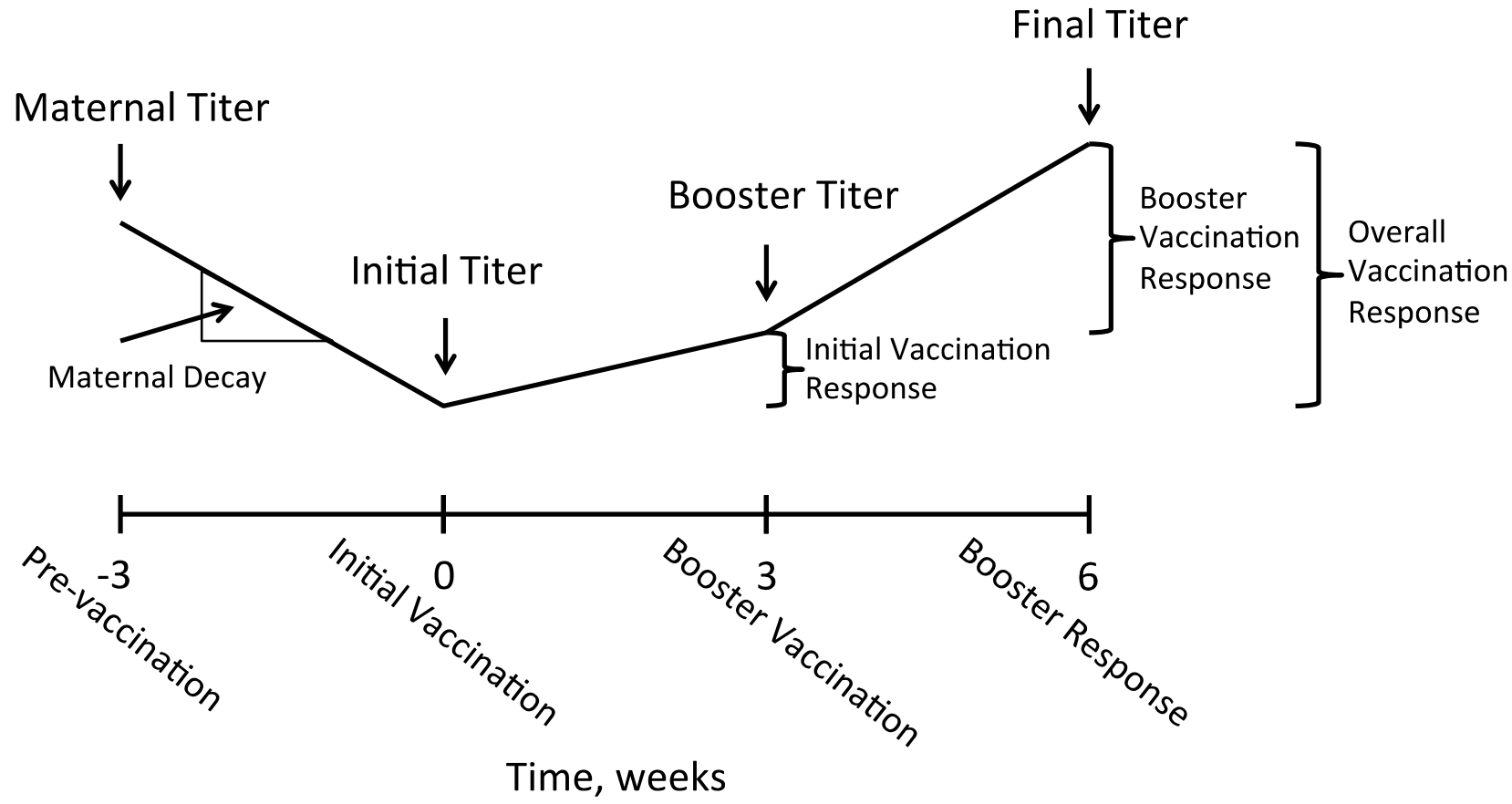

Final Titer
Maternal Titer
Booster Titer
Initial Titer
Booster Vaccination Response
Overall Vaccination Response
Initial Vaccination Response
Maternal Decay
-3
0
3
6
Pre-vaccination
Initial Vaccination
Booster Vaccination
Booster Response
Time, weeks

Figure 2:

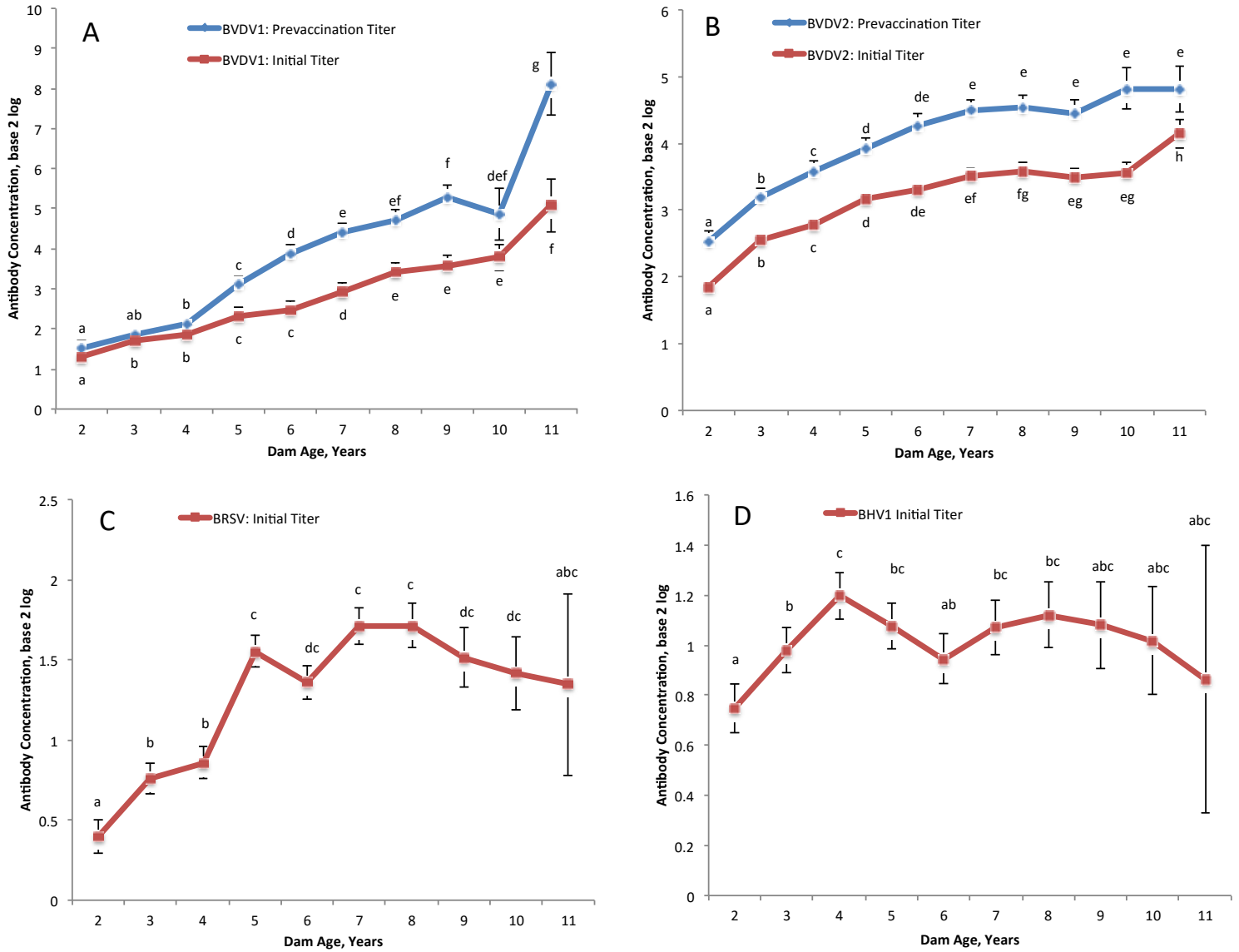

A
BVDV1: Prevaccination Titer
BVDV1: Initial Titer
Antibody Concentration, base 2 log
Dam Age, Years
B
BVDV2: Prevaccination Titer
BVDV2: Initial Titer
Antibody Concentration, base 2 log
Dam Age, Years
C
BRSV: Initial Titer
Antibody Concentration, base 2 log
Dam Age, Years
D
BHV1 Initial Titer
Antibody Concentration, base 2 log
Dam Age, Years

Figure 3:

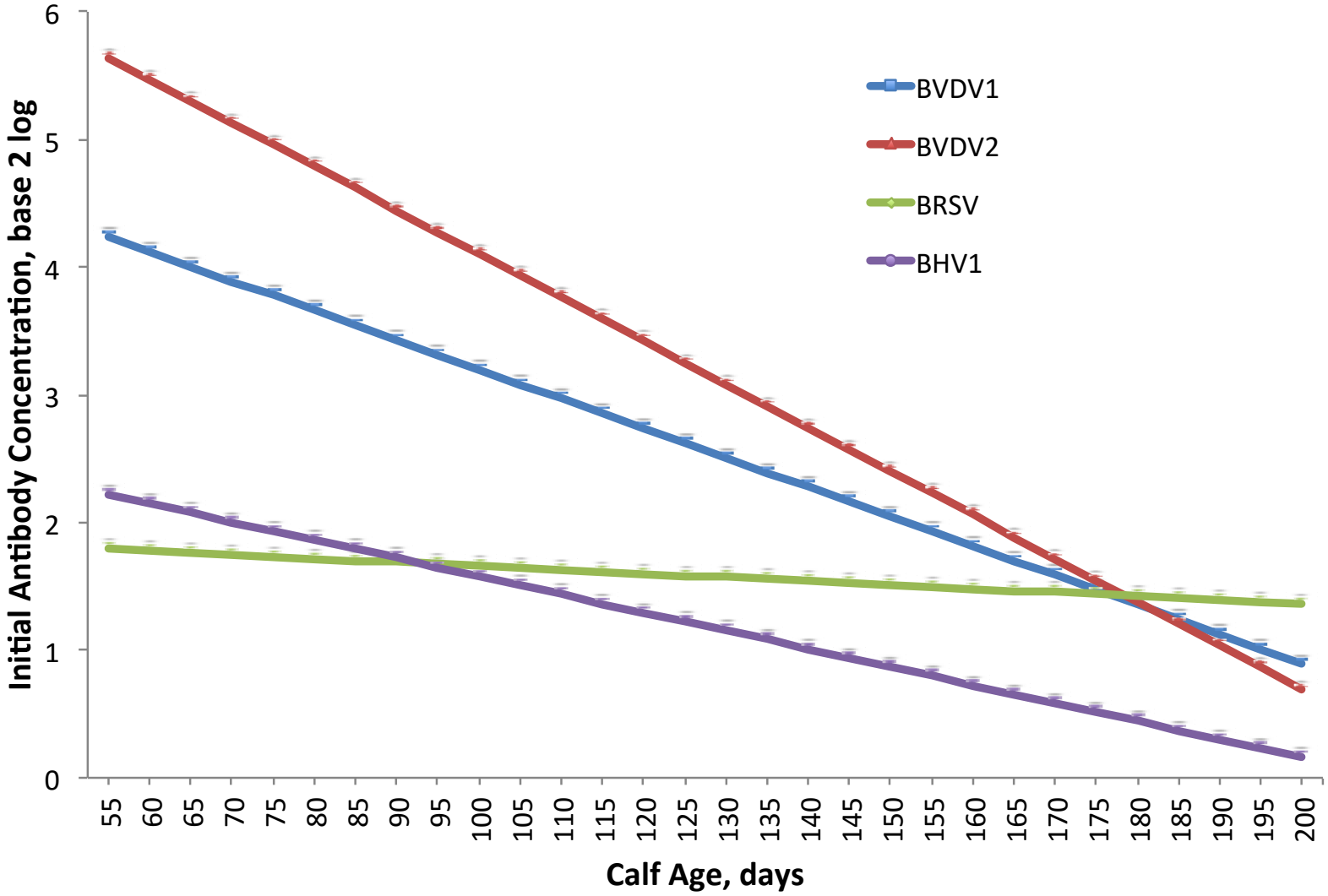

Initial Antibody Concentration, base 2 log
0
1
2
3
4
5
6
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
175
180
185
190
195
200
Calf Age, days
BVDV1
BVDV2
BRSV
BHV1

Figure 4:

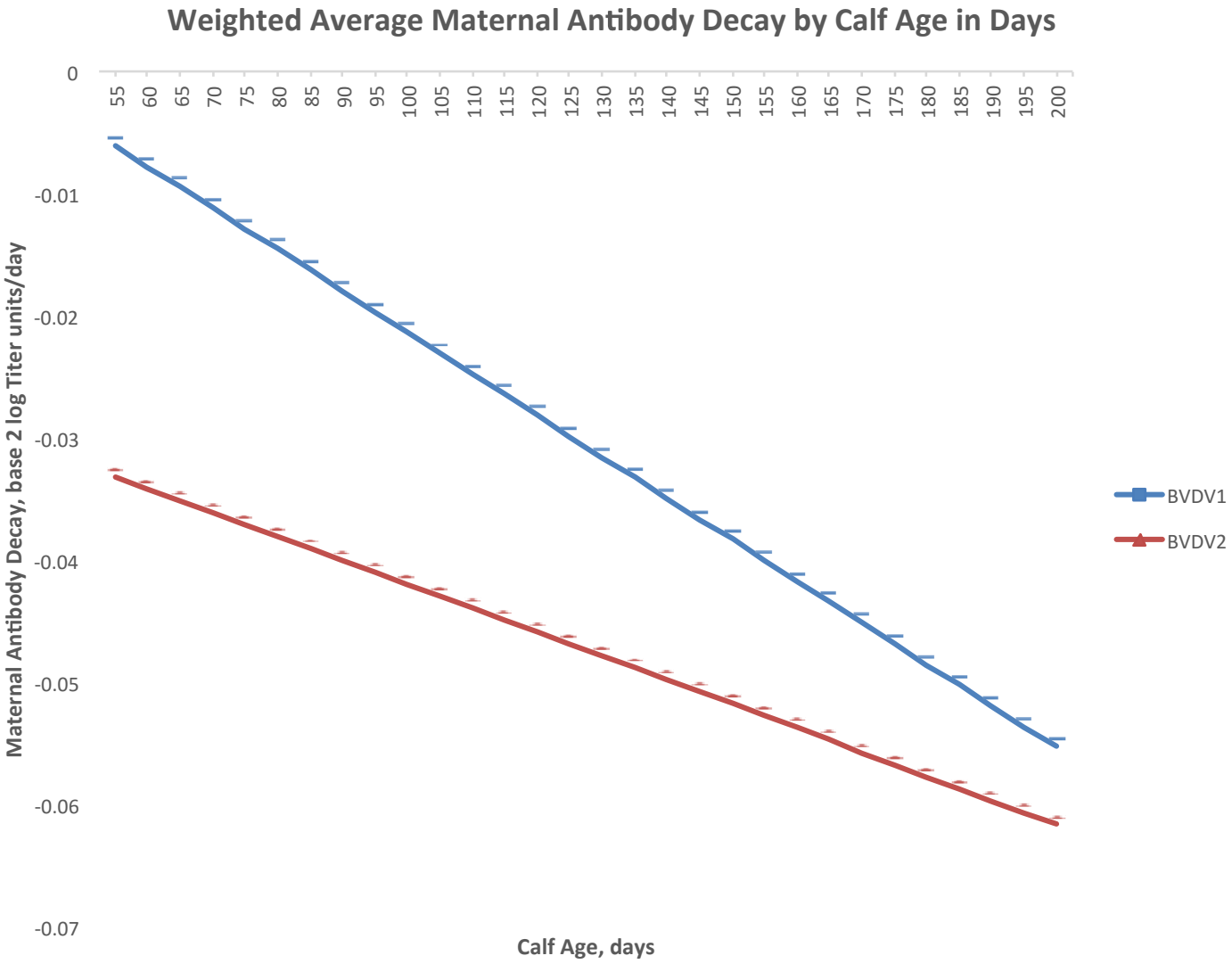

Weighted Average Maternal Antibody Decay by Calf Age in Days
0
-0.01
-0.02
-0.03
-0.04
-0.05
-0.06
-0.07
55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200
Maternal Antibody Decay, base 2 log Titer units/day
Calf Age, days
BVDV1
BVDV2

Figure 5:

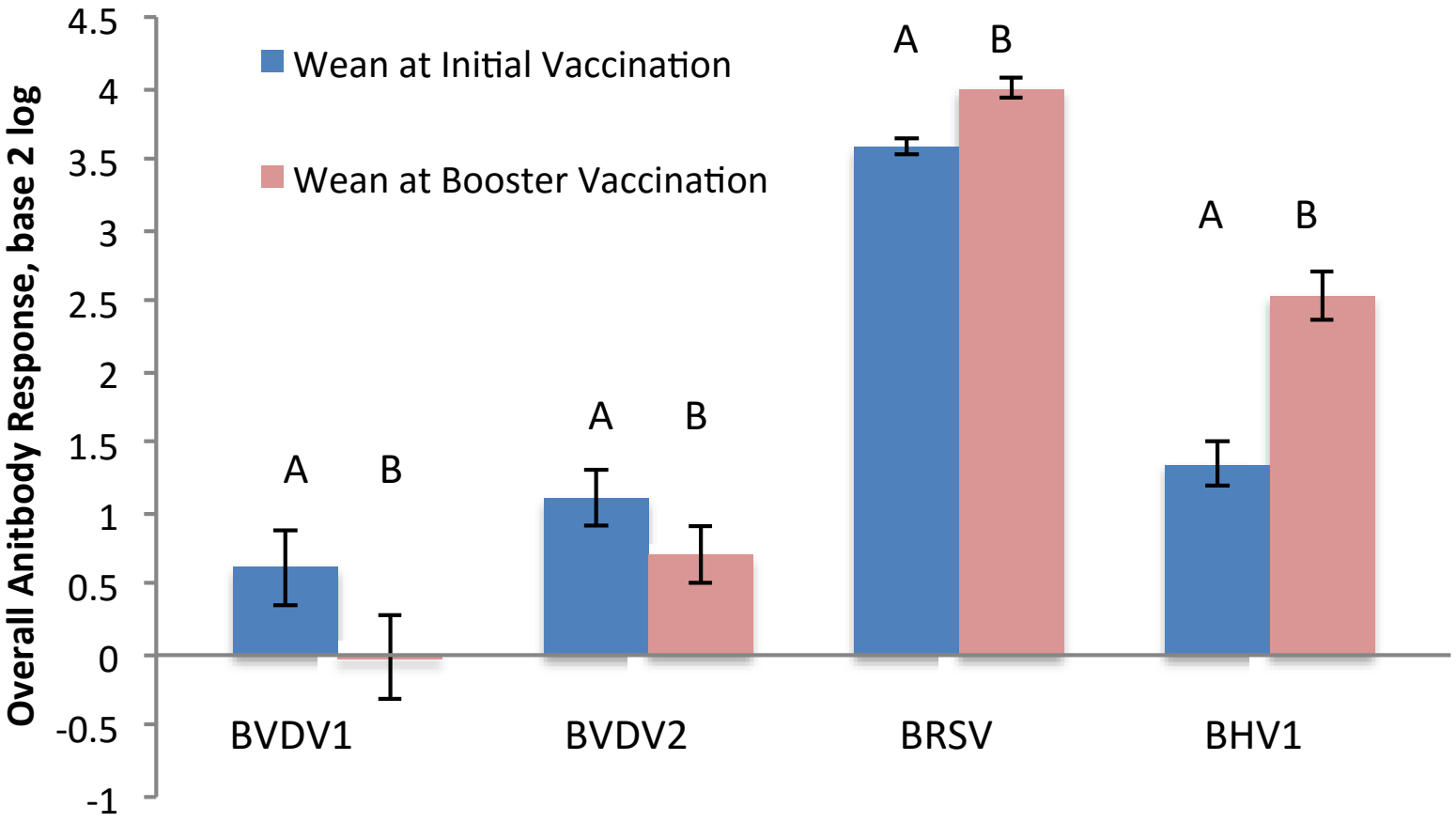

Overall Anitbody Response, base 2 log
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
-1
Wean at Initial Vaccination
Wean at Booster Vaccination
A
B
A
B
A
B
A
B
BVDV1
BVDV2
BRSV
BHV1

Figure 6:

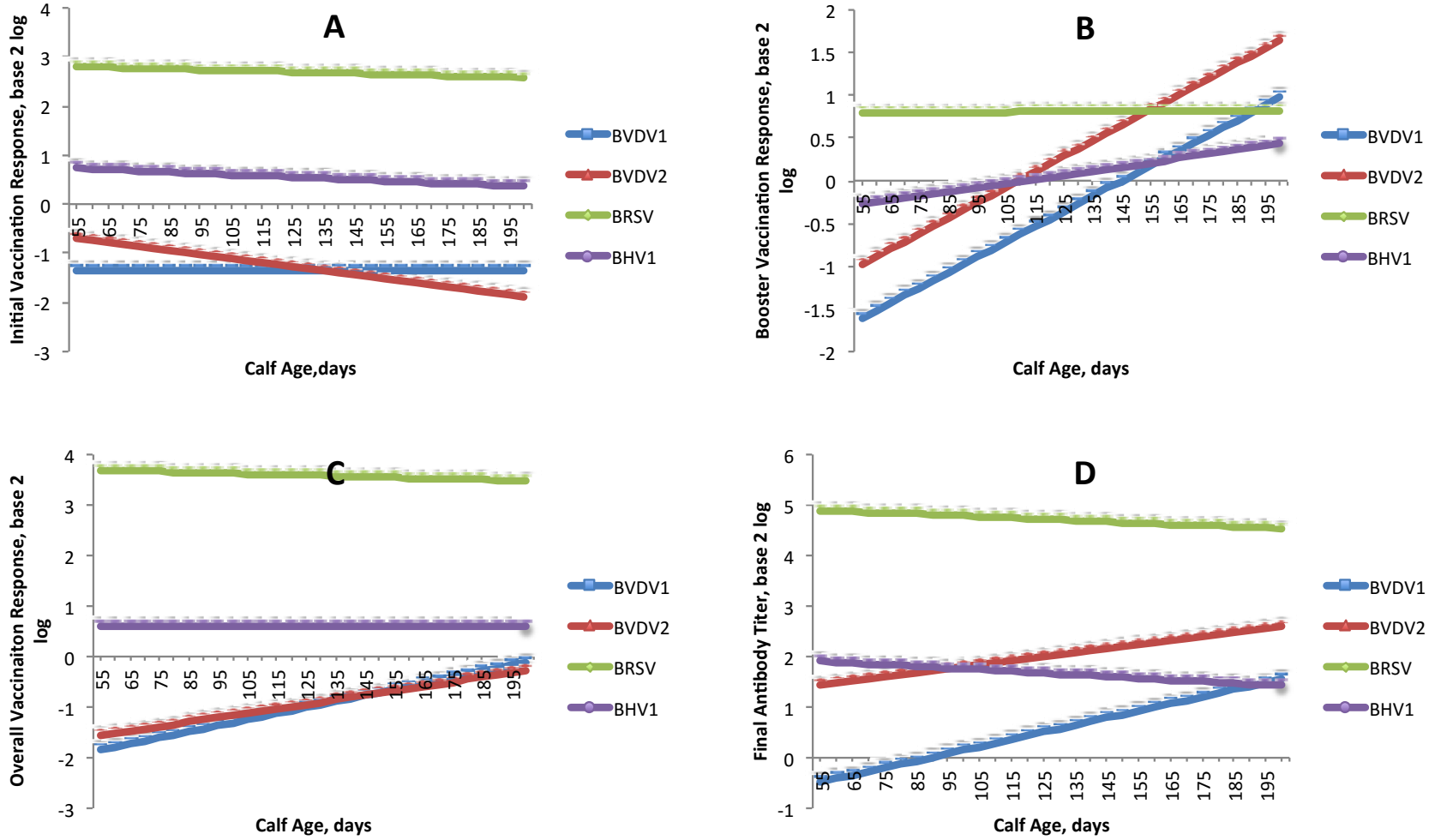

A
Initial Vaccination Response, base 2 log
Calf Age,days
BVDV1
BVDV2
BRSV
BHV1
B
Booster Vaccination Response, base 2 log
Calf Age, days
C
Overall Vaccinaiton Response, base 2 log
Calf Age, days
D
Final Antibody Titer, base 2 log
Calf Age, days

Figure 7:

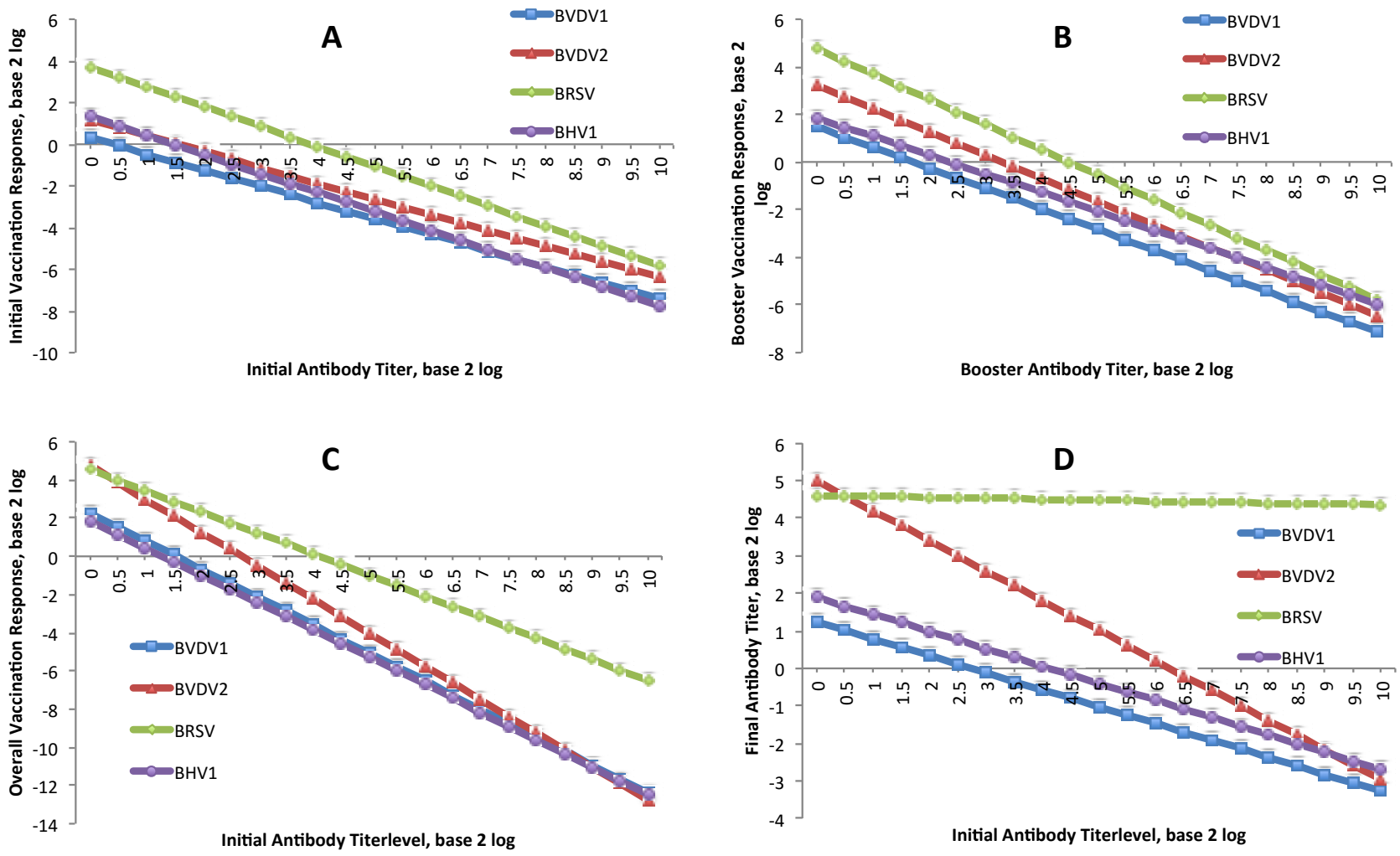

A
Initial Vaccination Response, base 2 log
Initial Antibody Titer, base 2 log
BVDV1
BVDV2
BRSV
BHV1
B
Booster Vaccination Response, base 2 log
Booster Antibody Titer, base 2 log
C
Overall Vaccination Response, base 2 log
Initial Antibody Titerlevel, base 2 log
D
Final Antibody Titer, base 2 log
Initial Antibody Titerlevel, base 2 log

Figure 8:

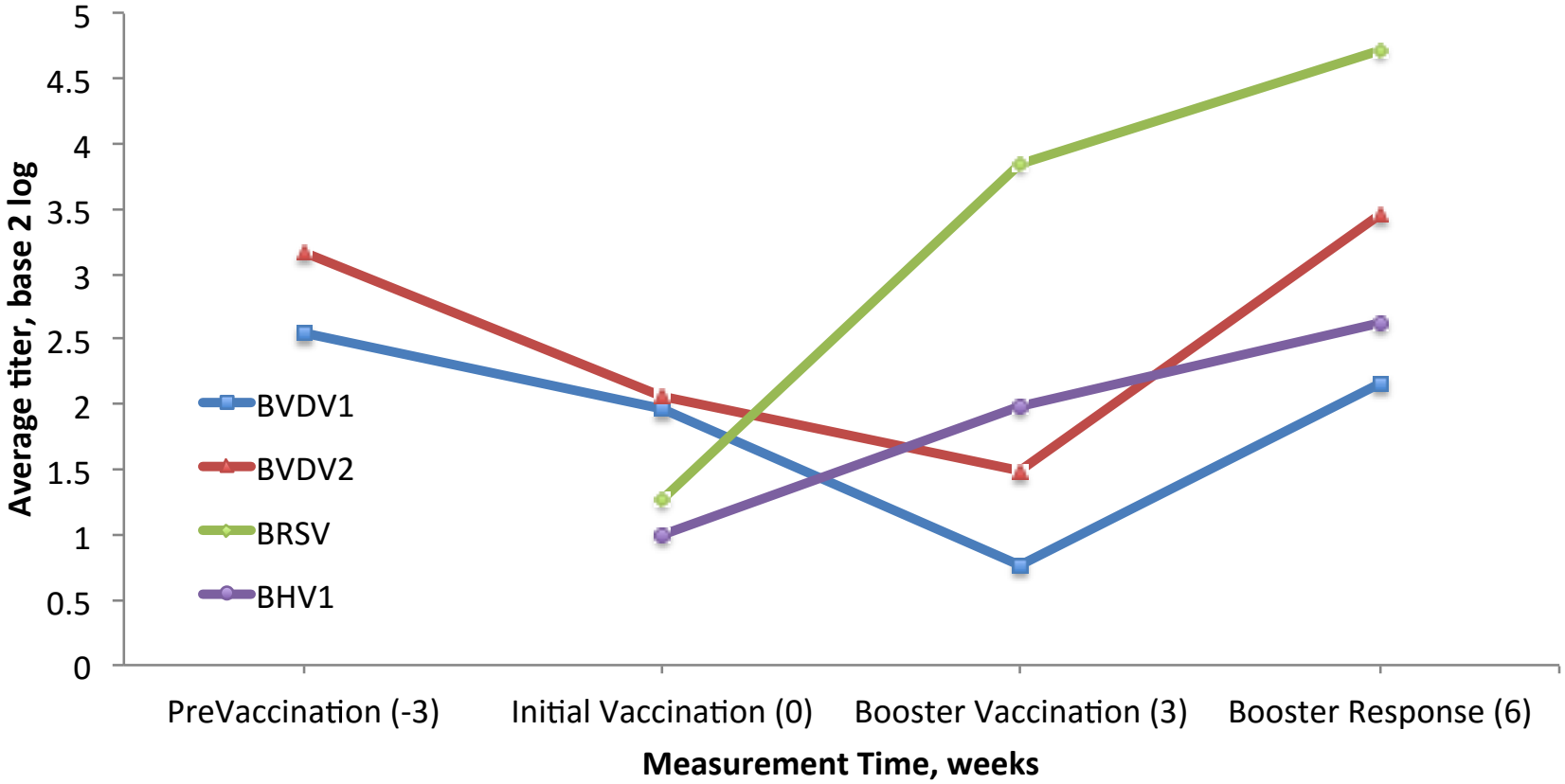

5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Average titer, base 2 log
BVDV1
BVDV2
BRSV
BHV1
PreVaccination (-3)
Initial Vaccination (0)
Booster Vaccination (3)
Booster Response (6)
Measurement Time, weeks

Figure 9:

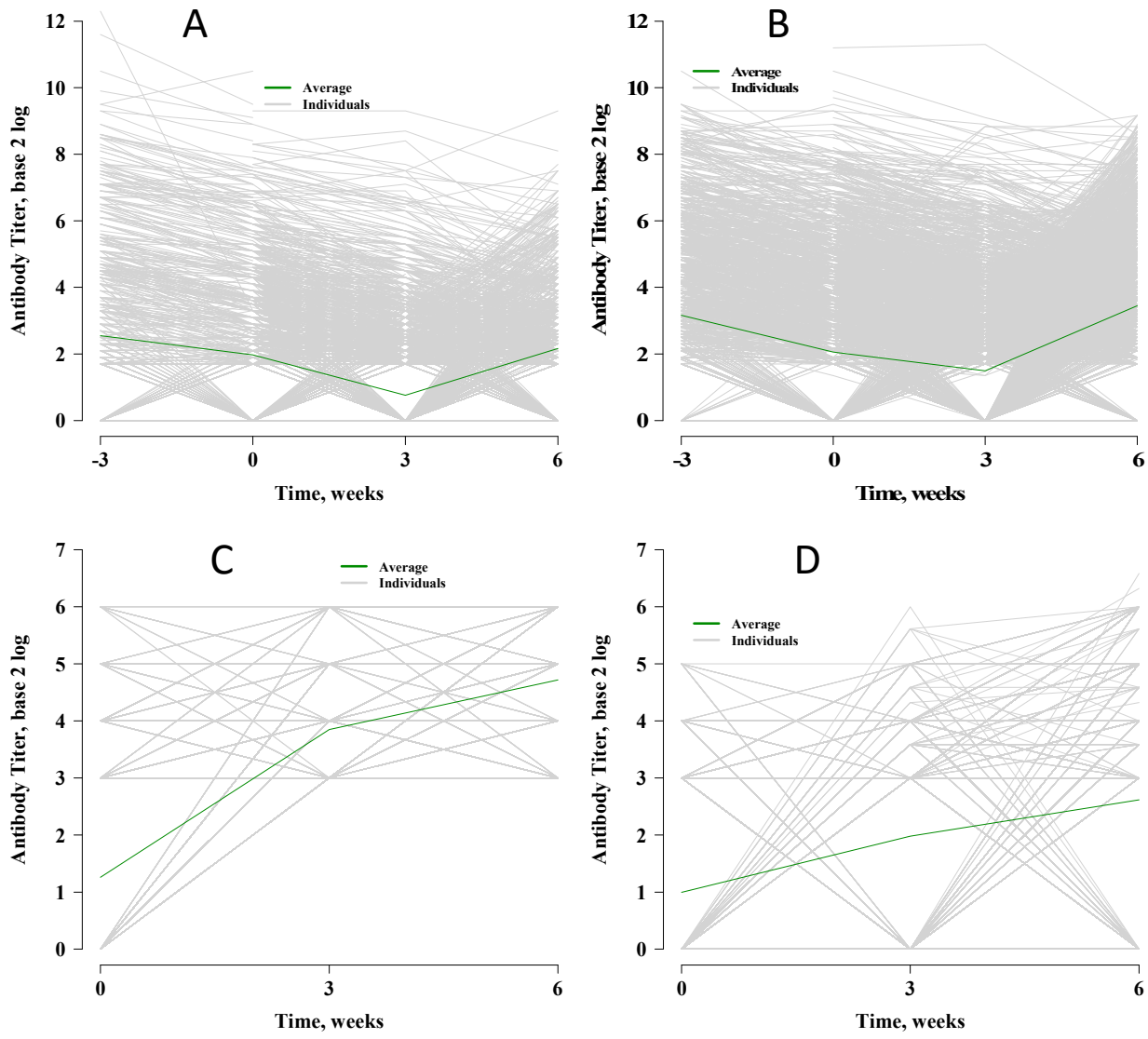

A
B
C
D
Average
Individuals
Antibody Titer, base 2 log
Time, weeks

Figure 10:

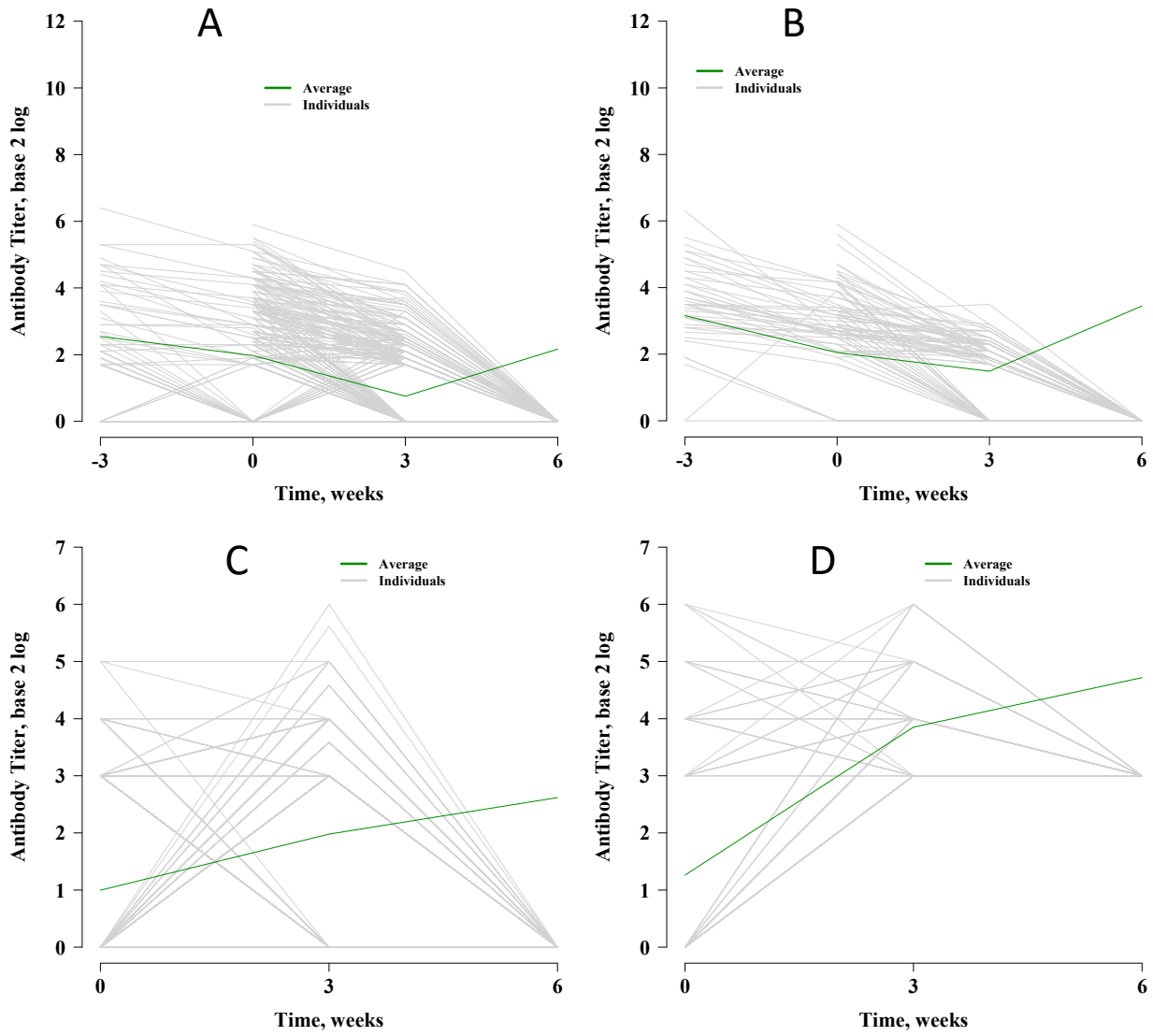
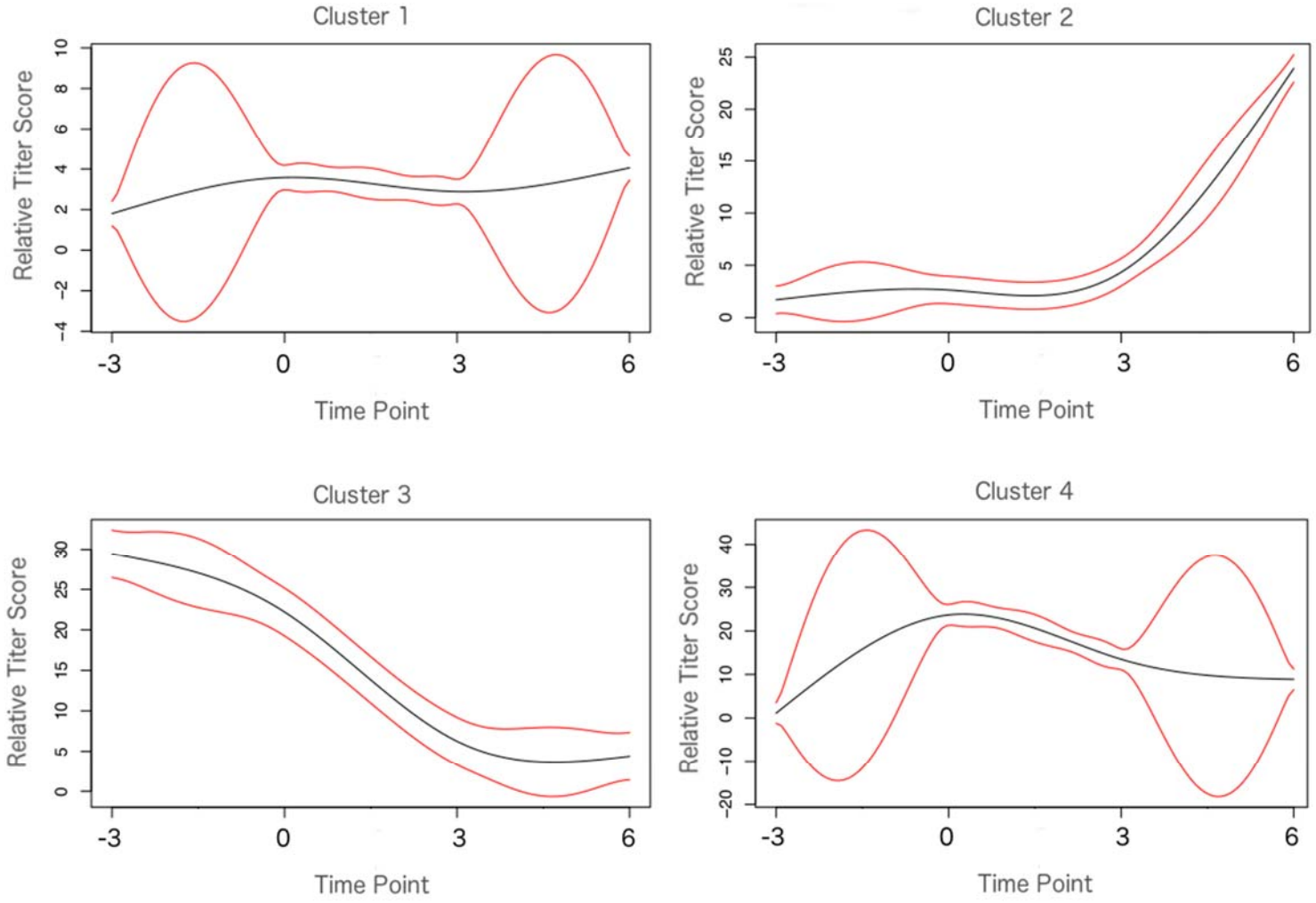

A
B
C
D
Average
Individuals
Antibody Titer, base 2 log
Time, weeks

Figure 11:


Cluster 1
Relative Titer Score
-4 -2 0 2 4 6 8 10
-3 0 3 6
Time Point
Cluster 2
Relative Titer Score
0 5 10 15 20 25
-3 0 3 6
Time Point
Cluster 3
Relative Titer Score
0 5 10 15 20 25 30
-3 0 3 6
Time Point
Cluster 4
Relative Titer Score
-20 -10 0 10 20 30 40
-3 0 3 6
Time Point

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